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High Patient Disease Burden in a Cross-sectional, Multicenter Contact Registry Study of Eosinophilic Gastrointestinal Diseases

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Abstract

Objectives: Clinical features of eosinophilic esophagitis (EoE) have been well-described in the literature, however, characterization of features experienced by patients with other eosinophilic gastrointestinal diseases (EGIDs) is lacking. Using data collected from a patient contact registry, we sought to characterize and contrast patient-reported gastrointestinal and extragastro-intestinal symptoms and comorbidities in non-EoE EGIDs, including eosinophilic gastritis, gastroenteritis and colitis, relative to EoE.

Methods: We conducted a cross-sectional study of contact registry data collected from 2015 to 2018. Statistical comparisons were made using chi-square (categorical measures) and the Mann-Whitney *U* test (continuous measures). Multivariable analyses were used to evaluate associations between treatment and feelings of isolation.

Results: Of the 715 reporting an EGID diagnosis (n = 525 EoE; n = 190 non-EoE EGID), a higher proportion of those with a non-EoE EGID reported more frequent specific and nonspecific gastrointestinal symptoms, including nausea, abdominal pain, diarrhea, constipation, and bloating *(P* < 0.01 for all). Participants with a non-EoE EGID were more likely to report higher frequency of fatigue, isolation, and deep muscle or joint pain (*P* < 0.01 for all). Specific food elimination and elemental formula treatments were associated with increased odds of more frequent (at least weekly) feelings of isolation for participants with EoE (adjusted odds rtaio [aOR]: 2.4; 95% confidence interval [CI]: 1.5–4.1 for specific food elimination and adjusted OR: 1.9; 95% CI: 1.2–3.3 for elemental formula).

Conclusions: Significant differences exist in the symptoms and comorbidities experienced between those with EoE versus non-EoE EGIDs. Additional investigation is needed to elucidate the factors that may contribute to the high disease burden of these poorly understood conditions.

Keywords

contact registry; eosinophilic colitis; eosinophilic esophagitis; eosinophilic gastritis; eosinophilic gastroenteritis; eosinophilic gastrointestinal disease

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Eosinophilic gastrointestinal diseases (EGIDs), including eosinophilic esophagitis (EoE), eosinophilic gastritis (EG), eosinophilic gastroenteritis (EGE), and eosinophilic colitis (EC) are rare, immune-mediated, gastrointestinal disorders associated with the presence of or increased burden of, tissue-specific eosinophilia, clinical features, and absence of other conditions associated with eosinophilia (1,2). As recently as just 2 decades ago, EGIDs were unrecognized conditions. The increase in incidence and prevalence of EoE, across these 2 decades, has been well-documented and the current prevalence is estimated to be ~50 to 100 cases/100,000. For the other non-EoE EGIDs, specifically EG, EGE, and EC, disease incidence remains rare, with an estimated 6.3 cases of EG/100,000, 5.1–8.4 cases/100,000 of

EGE, and 2.1 to 3.3 cases/100,000 of EC (2,3). As these conditions are uncommon, the patient burden for these conditions, especially the non-EoE conditions, is poorly described.

The Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR) (4,5) was formed to advance the clinical care for patients with EGIDs through conduct of research into these rare diseases. The Consortium is represented by members of the clinical and research communities, as well as patient advocacy groups (PAGs). During the formation of CEGIR, an online Contact Registry was established, through the infrastructure provided by the Rare Diseases Clinical Research Network (RDCRN) (6). The goals of the Contact Registry are to support CEGIR activities, specifically encouraging individuals with EGIDs to register to learn about CEGIR initiatives and promote enrollment in CEGIR-supported clinical and observational studies. Once registered, CEGIR Contact Registry registrants have the opportunity to complete a questionnaire designed to characterize patient-reported experiences as it relates to having an EGID. In the present study, we sought to use the data collected through the Contact Registry questionnaire from 2015 to 2018 to describe and compare patient-reported symptoms and comorbidities by EGID type, with an objective of informing patient-centered research questions and hypotheses for future studies of EGIDs.

METHODS

The RDCRN Contact Registry for CEGIR has been securely maintained by the CEGIR Data Management Coordinating Center (DMCC). The University of South Florida Institutional Review Board approved the administration of the patient-questionnaire as a component of the Contact Registry. Patient awareness of the CEGIR Contact Registry is promoted through clinical encounters with CEGIR investigators across 14 CEGIR clinical sites, patient advocacy meetings and communications, and social media sites (5).

The 25-item questionnaire was designed to collect patient-reported information on disease diagnoses, management, symptoms, and comorbidities, including reporting physician-diagnosed vitamin deficiencies. Prior to launch of the questionnaire, the questionnaire was pretested with a sample of 163 respondents. Questions with a poor or inconsistent response (relative to other measures) were refined to ensure more complete and accurate data capture. For diagnosis of an EGID, questionnaire respondents were prompted to report physician-diagnosed EGID(s). Gastrointestinal and extra-intestinal symptoms and comorbidities were assessed, including evaluation of the presence of psychosocial comorbidities. In instances where the individual with an EGID was <18 years of age, the questionnaire could be completed by an adult caregiver. Contact Registry participants were consented online for participation in the questionnaire and their demographic data (age, country, sex) from the registrant process were available for linkage to the questionnaire. These data were linked to the questionnaire data and descriptive data were generated on those Contact Registry participants who completed the questionnaire.

Primary Analyses

In our primary analyses, we first examined the distribution of Contact Registry participant demographics by EGID type. Assessment of differences in distribution of demographic features by EGID type (EoE vs EG, EGE, and/or EC with or without EoE) were made using

chi-square (for categorical measures) and the Mann-Whitney *U* test (for continuous measures). Next, we described participant-reported frequency of symptoms by EGID type. The number of participants with EG, EGE, or EC was relatively low as compared with EoE, thus, we combined these other EGIDs into a single group for evaluation of differences in the frequency of gastrointestinal and extra-gastrointestinal symptoms and comorbidities between EGID types (EoE only vs EG, EGE, or EC with or without EoE). Chi-square tests were used to evaluate differences in distribution of reported frequency of symptoms and comorbidities, with Fisher exact tests used when cell counts were sparse (<5).

Secondary Analyses

Noting a relatively high proportion of Contact Registry participants reporting frequent feelings of isolation, we conducted a secondary analysis to evaluate the association between EGID treatment approach and feelings of isolation. In bivariate analysis, we compared the distribution of weekly or daily feelings of isolation, versus less frequent feelings of isolation (monthly, infrequently, or never) by treatment type. We stratified results by age (<18 years and 18 years or older). Differences in the distribution of frequency of feelings of isolation, by treatment type, within categories of EoE only versus another EGID, and within age groups, were made using the chi-square test. Where data were sparse, the Fisher exact test was used. Generalized linear models (logit link, binomial distribution) were used to estimate the crude and adjusted odds of self-reported feelings of isolation in relation to disease treatment approach. Adjusted models accounted for frequency of diarrhea and food avoidance behaviors, as proxy measures of disease severity. Assessments were stratified by EGID type (EoE only vs 1 or more other EGIDs) and participant age (adult vs pediatric [<18 years] age groups). All analyses were based on complete case analysis.

RESULTS

Participant Demographic Characteristics by Eosinophilic Gastrointestinal Disease Type

Of the 1400 patients enrolled in the CEGIR Contact Registry, 52% (n = 725) provided consent for and responded to the Contact Registry questionnaire. Of these, 99% (n = 715) reported a diagnosis of an EGID. Most respondents reported a diagnosis of EoE only (n = 525 vs n = 210 with EG, EGE, and/or EC, with or without concomitant EoE). Significant differences in sex distribution were reported (57% male—EoE only vs 45% male—EG, EGE, and/or EC; $P < 0.01$). Median age at the time of survey was younger among those with EoE only versus EG, EGE, and/or EC (16 vs 19 years; $P = 0.01$) (Table 1).

Gastrointestinal Symptoms and Comorbidities by Eosinophilic Gastrointestinal Disease Type

Overall, participants reported frequent symptoms of nausea, upper and lower abdominal pain, bloating, constipation, and diarrhea, with nausea and upper abdominal pain indicated as the most frequently occurring symptoms overall (21% and 23%, respectively) (Table 2). Additionally, across nearly all symptoms reported, frequency of symptoms was higher among those with EG, EGE, or EC as compared with those with EoE only (Table 2). No significant difference in frequency of symptoms by EGID type were reported for chest pain (10–13% daily) ($P = 0.46$) or vomiting (11–16% daily) ($P = 0.18$). Vitamin deficiencies were

also commonly reported among those with EG, EGE, or EC, with 49.7% of participants indicating having been told by a physician that they had a vitamin deficiency, relative to 28% of those with EoE only ($P < 0.0001$). A diagnosis of concomitant gastroparesis was also more commonly reported among those with EG, EGE, or EC, with 27.3% of participants versus 13.4% of those with EoE only ($P < 0.0001$) (Table 2).

Extra-intestinal Symptoms, Comorbidities, and Psychosocial Burden

Daily frequency of extra-intestinal symptoms was reported by those with both EoE-only and those with EG, EGE, or EC. For example, 1 in 3 participants (33%) reported daily feelings of fatigue. Daily feelings of isolation were reported in 30% of participants. Those with a non-EoE EGID generally self-reported more frequent extra-intestinal symptoms, comorbidities, and psychosocial concerns (Table 3). No difference in frequency of joint dislocations was reported (13.1% for EoE only versus 16.4% for non-EoE EGID [$P = 0.30$]).

Secondary Analysis of Feelings of Isolation

Among adults with EoE only, a significantly higher proportion of those reporting weekly or daily feelings of isolation were treated with a specific food elimination approach as compared with those reporting less frequent feelings of isolation (80.6% vs 59.5%; $P < 0.01$). For both pediatric and adult Contact Registry questionnaire, respondents with EoE, elemental diet therapy was associated with increased frequency of weekly or daily feelings of isolation ($P = 0.04$ for <18 and $P = 0.02$ for ≥18) (Table 4). For participants with EG, EGE, and/or EC, increased frequency of feelings of isolation was only associated with use of a PPI, and this was only among adults ($P = 0.04$) (Supplementary Table 1, Supplemental Digital Content, http://links.lww.com/MPG/B867). After adjusting for food avoidance behaviors and frequency of diarrhea, specific food elimination and elemental formula treatments remained associated with increased odds of more frequent (≥weekly) feelings of isolation for participants with EoE only (adjusted odds ratio [OR]: 2.4; 95% confidence interval [CI]: 1.5–4.1 for specific food elimination and adjusted OR: 1.9; 95% CI: 1.2–3.3 for elemental formula) (Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/MPG/B867). There was no evidence of modification by age in any of the adjusted analyses ($P > 0.15$ for all).

DISCUSSION

A high proportion of patients with an EGID report experiencing comorbidities. These patients also report a high frequency of extra-gastrointestinal symptoms. Significant differences exist in the symptoms and comorbidities experienced between those with EoE only versus a non-EoE EGID(s), with more severe symptoms and higher frequency of comorbidities experienced by those with non-EoE EGIDs. The high frequency of co-occurrence of comorbidities has been reported elsewhere, particularly not only for atopic conditions but also for autoimmune conditions and connective tissue diseases (7–12).

Although there have been some limited reports of increased psychosocial symptoms in the setting of EoE (13), the high frequency of patient-reported psychosocial symptoms has not been previously reported for EG, EGE, and/or EC. Secondary analysis of the association

between treatment approaches and feelings of isolation suggest that choice of treatment may contribute to increased feelings of isolation. Our findings are consistent with evidence obtained from patients with other atopic conditions, suggesting that dietary restrictions may have psychosocial implications, particularly among adolescents (14). Dietary restrictions may also have implications on parent psychosocial well-being (15).

A limitation to this study is that participants self-selected for participation, thus, the experience of these patients may not be generalizable to all patients with EGIDs. The sex distribution of EoE is generally skewed toward males. We observed a higher proportion of females. In general, women are more likely to respond to questionnaires and the high proportion of women responding may reflect this self-selection. Conversely, for EG, EGE, and EC, no male predominance has been observed (2,11). Thus, for the other EGIDs, the questionnaire response reflected the sex ratio distribution reported elsewhere. The questionnaire, although developed through an iterative process to ensure comprehension and response completeness, was not a validated instrument for patient-reported outcomes. Self-reported diagnosis of an EGID condition, although described as a physician-indicated diagnosis, was not validated by the medical record, thus it is possible that some patients erroneously self-reported diagnosis of an EGID. Currently, there are, however, no agreed upon published guidelines for diagnosis of EG, EGE, EC, thus, even within medical-record-indicated diagnosis, there may be variability in what this diagnosis represents. Although some participants reported the presence of both EoE and another EGID, by definition esophageal eosinophilia in the presence of another EGID is not diagnosed as EoE, rather EG, EGE, or EC with esophageal involvement. A proportion of patients with an EoE diagnosis only reported blood in their stool, suggesting the possibility of undiagnosed, concomitant eosinophilic involvement elsewhere, other gastrointestinal comorbidities or misdiagnosis of EoE. Still, the high proportion of GI symptoms reported is consistent with other reports for EoE (16) and non-EoE EGIDs (17). The high proportion of patients reporting vitamin deficiencies should be evaluated to identify specific deficiencies, with establishment of whether these represent dietary avoidance behaviors or, possibly, altered absorption because of disease or use of PPIs.

Another limitation of this study is that it was cross-sectional and thus, the temporality of the association between treatment choice and feelings of isolation cannot be ascertained. Furthermore, diarrhea and food avoidance behaviors may serve as poor proxies for disease severity. Thus, the potential remains that feelings of isolation are explained by disease severity, as opposed to disease treatment. Regardless, the high proportion of self-reported, frequent feelings of isolation, merits further exploration as this may have implications for treatment adherence and patient well-being (18). Further, these patients experience unique challenges to care, including lack of or incomplete health insurance for elemental formulas and repeat endoscopies, potentially contributing to increased stress (19). Although outside the scope of the current study, information on pharmacologic or behavioral treatment approaches for psychosocial issues being experienced as a result of high disease burden could help inform mitigation approaches for patients.

This study has several strengths. The sample size is the largest to date to explore patient burden for EGIDs, in particular for EG, EGE, and/or EC (20). The other, non-EoE EGIDs

are relatively uncommon and remain poorly described and poorly understood. The questionnaire ascertained a wide breadth of patient-reported gastrointestinal and extra-intestinal symptoms and co-morbidities. The high frequency of extra-intestinal symptoms and comorbidities may generate new hypothesis for disease pathogenesis. A high prevalence of connective tissue disorders has been reported in the EGID population (10,21,22). Several, albeit nonspecific, extra-gastrointestinal symptoms associated with connective tissue disorders (rashes/urticaria, flushing, lightheadedness/passing out, and back pain) (23,24) were included on the questionnaire and, consistent with these reports, were frequently reported by contact registry participants. Although no significant difference was observed in reported frequency of joint dislocation in EoE patients (13.1%) relative to non-EoE EGIDs (16.4%), the frequency of joint dislocation was higher than that, which has been reported from emergency department data collected in the United States (23.9 cases per 100,000 patient years) (25). Direct measures of the incidence of connective tissue disorder in patients with EGIDs could be useful in establishing the need for additional clinical support for these conditions, especially as hypermobility with EoE has been reported (10). Heterogeneity in disease burden, according to concomitant connective tissue disease, should also be examined to assess whether these patients experience a more severe disease phenotype.

Additional investigation is needed to elucidate the factors that may contribute to the high disease burden of these poorly understood conditions. Novel treatment approaches that do not require highly restrictive diets would potentially help mitigate patient perception of disease burden. Holistic approaches and the application of additional patient care resources may be needed to address possible psychosocial factors that arise over the course of disease treatment. Identification of possible resilience factors or protective factors could provide insight into which patients may be at the highest risk of adverse psychosocial outcomes. The results of this study demonstrate need for research to mitigate patient burden associated with these conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What Is Known

- Eosinophilic esophagitis is increasingly common, but eosinophilic gastritis, gastroenteritis, and colitis remain uncommon and difficult to study.
- Eosinophilic gastrointestinal diseases necessitate, for some patients, challenging treatments, including restrictive and elemental diets.

What Is New

- Eosinophilic gastrointestinal diseases are associated with high, patient-reported burden, including frequency of feelings of isolation.
- Treatments, as well as disease severity, may contribute to patient burden.
- Eosinophilic gastritis, gastroenteritis or colitis, relative to eosinophilic esophagitis alone, are associated with higher patient burden.

TABLE 1.

Characteristics of patients completing Contact Registry Questionnaire

	EGID type		
Characteristic[†]	**EoE only, n = 525**	**EG, EGE, or EC,**[*] **n = 190**	***P***
Gender, n (%)			
Male	290 (57.1)	81 (45.3)	<0.01
Female	218 (42.9)	98 (54.8)	
Age at survey, median years (IQR)			
	16 (7, 35)	19 (10, 38)	0.01
Region, n (%)			
Africa	0 (0)	1 (0.6)	
Asia	0 (0)	2 (1.1)	<0.0001
Australia or New Zealand	17 (3.3)	3 (1.7)	
North America	481 (94.1)	157 (87.2)	
South America	0 (0)	3 (1.7)	
Europe	13 (2.5)	14 (7.8)	

EC= eosinophilic colitis; EG = eosinophilic gastritis; EGE = eosinophilic gastroenteritis; EGIDs = eosinophilic gastrointestinal diseases; EoE = eosinophilic esophagitis; IQR = interquartile range.

[*] With or without concomitant EoE.

[†] n = 4 missing gender; n = 2 missing age at survey; n = 24 missing region.

TABLE 2.

Gastrointestinal symptoms and comorbidities reported by eosinophilic gastrointestinal disease type

	EGID type		
Symptom/comorbidity	**EoE only, n (%)**	**EG, EGE, or EC,* n (%)**	***P***
Nausea			
Never	115 (22.8)	16 (9.3)	<0.0001
Infrequently/quarterly	104 (20.6)	29 (16.8)	
Monthly	93 (18.5)	20 (11.6)	
Weekly	111 (22.0)	44 (25.4)	
Daily	81 (16.1)	64 (37.0)	
Vomiting or regurgitation			
Never	102 (19.9)	25 (14.5)	0.18
Infrequently/quarterly	140 (27.3)	51 (29.7)	
Monthly	109 (21.3)	29 (16.9)	
Weekly	102 (19.9)	39 (22.7)	
Daily	59 (11.5)	28 (16.3)	
Chest pain			
Never	153 (30.4)	44 (25.3)	0.46
Infrequently/quarterly	104 (20.6)	41 (23.6)	
Monthly	93 (18.5)	33 (19.0)	
Weekly	106 (21.0)	33 (19.0)	
Daily	48 (9.5)	23 (13.2)	
Upper abdominal pain			
Never	98 (19.3)	18 (10.3)	<0.0001
Infrequently/quarterly	81 (15.9)	22 (12.6)	
Monthly	98 (19.3)	28 (16.0)	
Weekly	142 (27.9)	39 (22.3)	
Daily	90 (17.7)	68 (38.9)	
Lower abdominal pain			
Never	152 (29.9)	16 (9.3)	<0.0001
Infrequently/quarterly	88 (17.3)	16 (9.3)	
Monthly	97 (19.1)	34 (19.7)	
Weekly	104 (20.5)	51 (29.5)	
Daily	67 (13.2)	56 (32.4)	
Bloating			
Never	172 (34.0)	23 (13.1)	<0.0001
Infrequently/quarterly	98 (19.4)	26 (14.8)	
Monthly	76 (15.0)	29 (16.5)	
Weekly	96 (19.0)	45 (25.6)	
Daily	64 (12.7)	53 (30.1)	
Constipation			
Never	176 (34.9)	42 (24.1)	0.01

	EGID type		
Symptom/comorbidity	**EoE only, n (%)**	**EG, EGE, or EC,* n (%)**	***P***
Infrequently/quarterly	103 (20.4)	32 (18.4)	
Monthly	79 (15.6)	28 (16.1)	
Weekly	86 (17.0)	34 (19.5)	
Daily	61 (12.1)	38 (21.8)	
Diarrhea or loose stool			
Never	160 (31.5)	22 (12.6)	<0.0001
Infrequently/quarterly	104 (20.5)	28 (16.1)	
Monthly	93 (18.3)	33 (19.0)	
Weekly	107 (21.1)	44 (25.3)	
Daily	44 (8.7)	47 (27.0)	
Blood in stools			
No	393 (75.7)	87 (49.2)	<0.0001
Yes	99 (19.1)	74 (41.8)	
Do not know	27 (5.2)	16 (9.0)	
Vitamin deficiencies			
No/unknown	394 (72.0)	94 (50.3)	<0.0001
Yes	153 (28.0)	93 (49.7)	
Weight loss			
No	256 (49.3)	58 (32.8)	0.001
Yes	248 (47.8)	113 (63.8)	
Do not know	15 (2.9)	6 (3.4)	
Gastroparesis			
No/unknown	474 (86.7)	136 (72.7)	<0.0001
Yes	73 (13.4)	51 (27.3)	

EC= eosinophilic colitis; EG = eosinophilic gastritis; EGE = eosinophilic gastroenteritis; EGIDs = eosinophilic gastrointestinal diseases; EoE = eosinophilic esophagitis.

*With or without concomitant EoE.

TABLE 3.

Extragastrointestinal symptoms, comorbidities, and psychosocial burden reported by eosinophilic gastrointestinal disease type

	EGID type		
Symptom/comorbidity	**EoE only, n (%)**	**EG, EGE, or EC,* n (%)**	***P***
Extra-gastrointestinal symptoms and comorbidities			
Lightheadedness or passing out			
Never	285 (56.3)	57 (33.1)	
Infrequently/quarterly	89 (17.6)	32 (18.6)	<0.0001
Monthly	60 (11.9)	32 (18.6)	
Weekly	57 (11.3)	27 (15.7)	
Daily	15 (3.0)	24 (14.0)	
Deep muscle or joint pain			
Never	212 (41.7)	38 (21.7)	
Infrequently/quarterly	71 (14.0)	24 (13.7)	<0.0001
Monthly	70 (13.8)	17 (9.7)	
Weekly	86 (16.9)	36 (20.6)	
Daily	68 (13.4)	59 (33.7)	
Rashes or urticaria			
Never	256 (50.9)	63 (35.6)	0.02
Infrequently/quarterly	97 (19.3)	44 (24.9)	
Monthly	70 (13.9)	30 (17.0)	
Weekly	42 (8.4)	24 (13.6)	
Daily	37 (7.4)	16 (9.0)	
Joint dislocations			
No	417 (81.6)	135 (76.3)	0.30
Yes	67 (13.1)	29 (16.4)	
Do not know	27 (5.3)	13 (7.3)	
Flushing			
Never	293 (58.7)	63 (36.4)	<0.0001
Infrequently/quarterly	71 (14.2)	27 (15.6)	
Monthly	66 (13.2)	22 (12.7)	
Weekly	49 (9.8)	36 (20.8)	
Daily	20 (4.0)	25 (14.5)	
Psychosocial burden factors			
Feelings of isolation			
Never	75 (14.6)	11 (6.4)	<0.0001
Infrequently/quarterly	127 (24.8)	26 (15.0)	
Monthly	62 (12.1)	18 (10.4)	
Weekly	119 (23.2)	44 (25.4)	
Daily	130 (25.3)	74 (42.8)	
Fatigue			

	EGID type		
Symptom/comorbidity	**EoE only, n (%)**	**EG, EGE, or EC,* n (%)**	***P***
Never	126 (24.7)	12 (6.8)	<0.0001
Infrequently/Quarterly	65 (12.8)	16 (9.1)	
Monthly	77 (15.1)	21 (11.9)	
Weekly	115 (22.6)	28 (15.9)	
Daily	127 (24.9)	99 (56.3)	

EC= eosinophilic colitis; EG = eosinophilic gastritis; EGE = eosinophilic gastroenteritis; EGIDs = eosinophilic gastrointestinal diseases; EoE = eosinophilic esophagitis; IQR = interquartile range.

*With or without concomitant EoE.

TABLE 4.

Frequency of feelings of isolation by treatment and age for respondents with eosinophilic esophagitis only

	Age <18			Age ≥18		
	Never, infreq., or monthly, n (%)	Weekly or daily, n (%)	*P*	Never, infreq., or monthly, n (%)	Treatment type	*P*
PPI						
No	15 (15.0)	11 (9.2)	0.19	23 (19.5)	15 (16.0)	0.51 **
Yes	85 (85.0)	108 (90.8)		95 (80.5)	79 (84.0)	
Specific food elimination						
No	14 (12.4)	8 (6.5)	0.12	51 (40.5)	19 (19.4)	<0.01
Yes	99 (87.6)	116 (93.6)		75 (59.5)	79 (80.6)	
Topical/swallowed steroids						
No	21 (21.2)	31 (26.3)	0.38	35 (30.2)	29 (31.5)	0.83
Yes	78 (78.8)	87 (73.7)		81 (69.8)	63 (68.5)	
Systemic steroids						
No	74 (82.2)	84 (73.7)	0.15	93 (86.1)	68 (80.0)	0.26
Yes	16 (17.8)	30 (26.3)		15 (13.9)	17 (20.0)	
Mast cell stabilizer agents						
No	57 (66.3)	68 (58.6)	0.27	77 (72.6)	56 (63.6)	0.18
Yes	29 (33.7)	48 (41.4)		29 (27.4)	32 (36.4)	
Immunomodulatory agents						
No	82 (98.8)	106 (94.6)	0.24 *	95 (96.9)	79 (96.3)	0.82 *
Yes	1 (1.2)	6 (5.4)		3 (3.1)	3 (3.7)	
Elemental diet						
No	88 (76.5)	81 (64.3)	0.04	123 (95.4)	87 (87.0)	0.02
Yes	27 (23.5)	45 (35.7)		6 (4.7)	13 (13.0)	

* Fisher's exact test.

** Proton Pump Inhibitor.